Prevalence of Elevated Pulmonary Arterial Pressures Measured by Echocardiography in a Multicenter Study of Patients with Systemic Sclerosis

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ABSTRACT. ***Objective.*** To estimate the prevalence of elevated pulmonary arterial pressures (PAP) as a correlate for pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc) in rheumatology centers in Canada.

Methods. During the one-year study period (June 2002–May 2003), charts of patients with SSc were reviewed to determine demographics, SSc characteristics, percentage of patients with a PAH diagnosis, and the site criteria for such diagnosis. Subjects with no PAH that had symptoms of dyspnea and/or fatigue were invited to undergo Doppler echocardiography to estimate their systolic PAP (sPAP).

Results. A total of 539 patients with SSc (age 56 yrs ± 13 SD, 84% female, 41% with diffuse SSc, 58% limited SSc, SSc disease duration 9 yrs ± 7 SD) at 8 rheumatology centers were reviewed. Twenty-three percent of patients were diagnosed with elevated sPAP based on the site diagnosis criteria (i.e., > 30 mm Hg or > 35 mm Hg). From the non-PAH, not recently screened patients that had symptoms of dyspnea or fatigue, a total of 89 patients underwent a Doppler echocardiograph; 40% had sPAP > 35 mm Hg.

Conclusion. Elevated PAP are common in both limited and diffuse SSc disease, occurring in 21% of limited and 26% of diffuse SSc patients. During the screening most patients had mild PAP elevations that would require further assessments such as right heart catheterization to diagnose PAH where appropriate. A high index of suspicion is important and routine echocardiography in symptomatic patients may allow earlier diagnosis of PAH and intervention. The proportion of SSc patients with mild to moderate elevations of PAP who will develop significant PAH is unknown and longterm studies are needed to address the natural progression. (J Rheumatol 2005;32:1273–8)

Key Indexing Terms:
PULMONARY ARTERIAL PRESSURE PULMONARY ARTERIAL HYPERTENSION
SYSTEMIC SCLEROSIS SCLERODERMA PREVALENCE ECHOCARDIOGRAPHY

Systemic sclerosis (SSc) is a multisystem disorder characterized by collagen deposition and subsequent fibrosis of skin, blood vessels, and internal organs including the gastrointestinal tract, lungs, heart, and kidneys[1-3]. The disease can be classified into 2 main categories, limited or diffuse, based primarily on the degree of skin involvement[4]. SSc is a relatively rare disease with varying data on incidence and prevalence[5], with an incidence range from 2 to 20 per million population per year[5-7]. Incidence rates peak in the third to fifth decade, and the prevalence is higher in women, with a female to male ratio of roughly 3:1[6,7]. Prevalence rates vary widely: from 13 to 280 cases per million adults[6,8-11]. SSc is associated with a significantly increased mortality risk[12-16]. In Canada, Lee, *et al*[14] reported 3, 6, and 9-year

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survival rates of 86%, 76%, and 61%, respectively, in a population of patients attending a scleroderma clinic. A significant cause of scleroderma related mortality for both limited and diffuse disease is pulmonary arterial hypertension (PAH)[17,18]. PAH results from an increase in pulmonary vascular resistance or pulmonary blood flow and, regardless of the underlying cause, can lead to right ventricular failure and death[19]. Unfortunately, the diagnosis is often delayed, as patients commonly exhibit nonspecific symptoms, minimal signs on physical examination, and normal chest radiographs[20]. Historically, the only way to evaluate the presence of PAH was through right heart catheterization, an invasive technique associated with some degree of risk. However, Doppler echocardiography (DEC) is a noninvasive way of assessing pulmonary artery pressure (PAP) based on the velocity of the tricuspid regurgitant jet, correlating with values obtained using right heart catheterization[18].

However, the correlation between PAP measurement with echocardiography and right heart catheterization is not 100%, and in some patients PAP cannot be estimated by echocardiography (i.e., absence of tricuspid regurgitation). Also, the reliability of PAP at > 50 mm Hg on echocardiography compared to right heart catheterization is better than a cutoff between 30 and 40 mm Hg. Despite the limitations, DEC has been used to screen for elevated PAP in SSc. The reported prevalence of PAH in scleroderma has also shown wide variation, from 4.9% to 35%[20,21], depending on the methodology, population, and definition of PAH used. SSc patients with PAH have a very poor prognosis, with reported survival rate of only 40%–55% at 2 years when PAP are increasing[21,22]. Thus, the current World Health Organization (WHO) 1998 recommendation for SSc patients is to screen for PAH annually with a transthoracic echocardiogram[23]. Screening has become more important recently with the availability of effective treatments such as epoprostenol[24] and bosentan[25].

Study rationale and objectives. There are currently no accurate multicenter data on the prevalence of pulmonary hypertension among patients with scleroderma in Canada. Further, there are limited published data on local practices for its detection and diagnosis. This study was designed to address these issues by assessing how many SSc patients are currently screened for PAH in Canada, the current proportion diagnosed with elevated PAP, and the potential frequency of high PAP in a symptomatic SSc population.

MATERIALS AND METHODS

Patient population. The patient population consisted of SSc patients receiving care at rheumatology centers in Canada. There were no specific requirements for patient age, sex, or disease severity or duration. The primary care physician was not necessarily the investigator. Ethics committee approval was obtained at each site.

Patients included in the study required a diagnosis of scleroderma [as defined by the American College of Rheumatology (ACR) classification criteria], or CREST (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome if they did not fulfill ACR preliminary criteria for scleroderma[4]. They had to be alive for at least part of the 12-month study period (June 2002–May 2003). For the retrospective portion of the study, patients required a diagnosis of pulmonary hypertension or elevated PAP as determined by site-specific criteria. In the prospective part of the study, patients not previously identified as having PAH who had not had an echocardiogram performed after December 2001 were required to have symptoms of dyspnea or fatigue (from a dyspnea-fatigue questionnaire) and to provide consent to receive a DEC. Patients with mixed connective tissue disease (with features of systemic lupus erythematosus, systemic sclerosis, polymyositis, and rheumatoid arthritis, together with high circulating levels of antibody to nuclear ribonucleoprotein antigen) or overlap scleroderma syndromes were excluded from the study.

Design. The study involved both retrospective and prospective components. For each SSc patient's chart reviewed, the data collected included sex, year of birth, type of SSc, date of SSc or CREST diagnosis, and history of echocardiogram performed since time of SSc diagnosis. By retrospective chart review, a prevalence of elevated PAP in scleroderma was estimated based on site-determined criteria. Additional data collected from patients with elevated PAP included race, date of PAH diagnosis, type of PAP elevation (isolated or secondary to interstitial lung disease), results of relevant investigations [including echocardiogram, right heart catheterization, pulmonary function, skin score, computerized tomography (CT) scan, and chest radiograph], history of digital ulcers, presence of Scl-70 and anticentromere antibodies, symptoms prior to PAH diagnosis, and PAH treatment.

In the prospective component of the study an adjusted prevalence was determined by administering a DEC to patients having dyspnea and/or fatigue symptoms drawn from a pool of untested SSc patients. By combining the proportion of SSc patients with elevated PAP, as assessed by site testing criteria, and the proportion of patients with abnormal systolic pulmonary arterial pressure (sPAP; > 35 mm Hg) evaluated by DEC in the untested, consenting, symptomatic patient population, an overall adjusted prevalence of elevated PAP was determined.

Endpoints. The primary endpoint of the study was the estimated prevalence of elevated PAP in SSc patients, including the current proportion with elevated PAP and the proportion of untested/not screened symptomatic SSc patients having a high PAP as assessed by DEC. Secondary endpoints included relative distribution of elevated PAP in limited and diffuse SSc; the type and criteria of tests used for PAH diagnosis; relative distribution of isolated PAP elevations and secondary PAP elevations from interstitial lung disease; and current treatment patterns.

RESULTS

A total of 539 patients at 8 rheumatology centers were studied; the mean age was 56 ± 13 SD years (range 16–87 yrs), and the mean time from SSc diagnosis was 9 ± 7 years (range 0–43 yrs). Two hundred twenty-one patients had diffuse SSc (41% of the study population), while 312 had limited disease (fulfilling either ACR criteria or criteria for CREST; 57.9%). A further 1.1% did not have disease type documented.

Primary endpoint. Of 539 patients entering the study, 124 had a diagnosis of elevated PAP (23%). Of the 8 centers, 5 used DEC as the primary diagnostic tool, while the other 3 used a combination of DEC and right heart catheterization to diagnose PAP. There was wide variability among centers in this study, with a low incidence of 8.6% at one center and a high of 52% (Table 1). Data from the retrospective chart review of all 124 patients with high PAP are shown in Figure 1. In summary, 44% of the subjects (n = 54) who had chart

Table 1. Prevalence (as diagnosed by the center-specific criteria) of elevated pulmonary arterial pressure (PAP) in systemic sclerosis (SSc) by participating center.

Center	No. of SSc Patients	Percentage of SSc with Elevated PAP	Test for PAH
1	54	18.5	DEC
3	9	33.3	DEC
4	41	24.4	DEC
5	121	12.4	DEC
6	178	19.7	DEC + RHC
7	25	52.0	DEC
9	35	8.6	DEC + RHC
10	76	46.1	DEC + RHC

DEC: Doppler echocardiography, RHC: right heart catheterization.

review had a PAP of 30–40 mm Hg, 36% (n = 44) had PAP of 41–60 mm Hg, and 20% (n = 25) had PAP of at least 60 mm Hg. The mean duration since PAH diagnosis was 39 ± 32 months (range 6–153 mo), and 19.4% (n = 20) had documentation of right heart dilation.

Of 539 patients entering the study, 307 were identified as not having elevated PAP and had not been tested by DEC after December 2001. We were able to contact 237 from this cohort, and 122 patients had symptoms of dyspnea and/or fatigue. Of the symptomatic patients, 89 (73%) agreed to DEC testing and 36 of the 89 (40%) were found to have sPAP > 35 mm Hg (including 8 patients with an estimated PAP > 45 mm Hg and one > 60 mm Hg). This subsequent testing resulted in an additional 6% from the total SSc cohort found to have elevated PAP and potentially some with significant PAH. Figure 2 shows the distribution of subjects included in the study.

Secondary endpoints. The demographics of those with elevated PAP were as follows. There were 124 with elevated PAP, of whom 108 (87.1%) were women, 107 (86%) were Caucasian; the mean age was 59.2 years (range 27–87 yrs), similar to the overall SSc population. The mean time from the diagnosis of SSc to diagnosis of elevated PAP was 7.7 years, being greater in the subpopulation with limited SSc (8 years) than in those with diffuse SSc (7.2 years).

The majority of patients with elevated PAP were found to have isolated disease [68/124 (54.8%)], while the incidence of elevated PAP secondary to fibrosis was 29.8%. An etiology was not determined in 15.3% of cases (Figure 3). A diagnosis of secondary elevated PAP was made if the total lung capacity was < 70% of the predicted value, or there was CT scan evidence of diffuse interstitial fibrosis or alveolitis, or there was evidence of significant obstructive lung disease with a FEV1/FVC ratio < 50%.

Elevated PAP occurred in 58 of 221 (26.2%) patients with diffuse SSc and in 66 of 312 (21.2%) with limited SSc. The average age of patients in the diffuse SSc population was lower than in the limited group (56.3 years vs 61.8 yrs, respectively).

The incidence of digital ulcers was common in both groups of SSc patients diagnosed with PAH (limited 54.4% and diffuse 58.6%). We did not collect data on digital ulcer history in the overall scleroderma population, so we could not determine if prevalence of digital ulcers was more associated with PAH.

In terms of testing, it was determined that 43% of all SSc patients in the study had not undergone an echocardiogram since their diagnosis, likely because historically specific treatment for PAH in scleroderma was not readily available. For the 57% of the patients that had undergone DEC, the mean number of echocardiograms per patient was 2.27. The tests performed for those with elevated PAP since the time of their SSc diagnosis included pulmonary function testing (in 88%), chest radiograph (72%), CT scan (50%), skin score (32%), and right heart catheterization (10%).

Seventy-seven percent of the patients with elevated PAP were tested for diffusing capacity for carbon monoxide (DLCO). Of those tested, 89% had abnormal results and 58% had DLCO lower than 60% of predicted.

In terms of treatment, a large proportion (72%) of patients with elevated PAP were not receiving PAH-specific

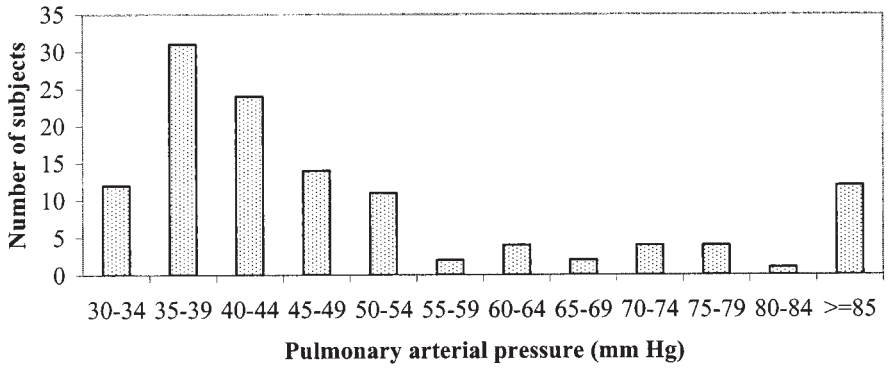

Figure 1. Frequency of pulmonary arterial pressure results for study subjects (n = 121). The results for all sites have been pooled. Values from 3 subjects (Site 1) have not been shown in the data as they were reported as mild or moderate, but with no associated numeric value.

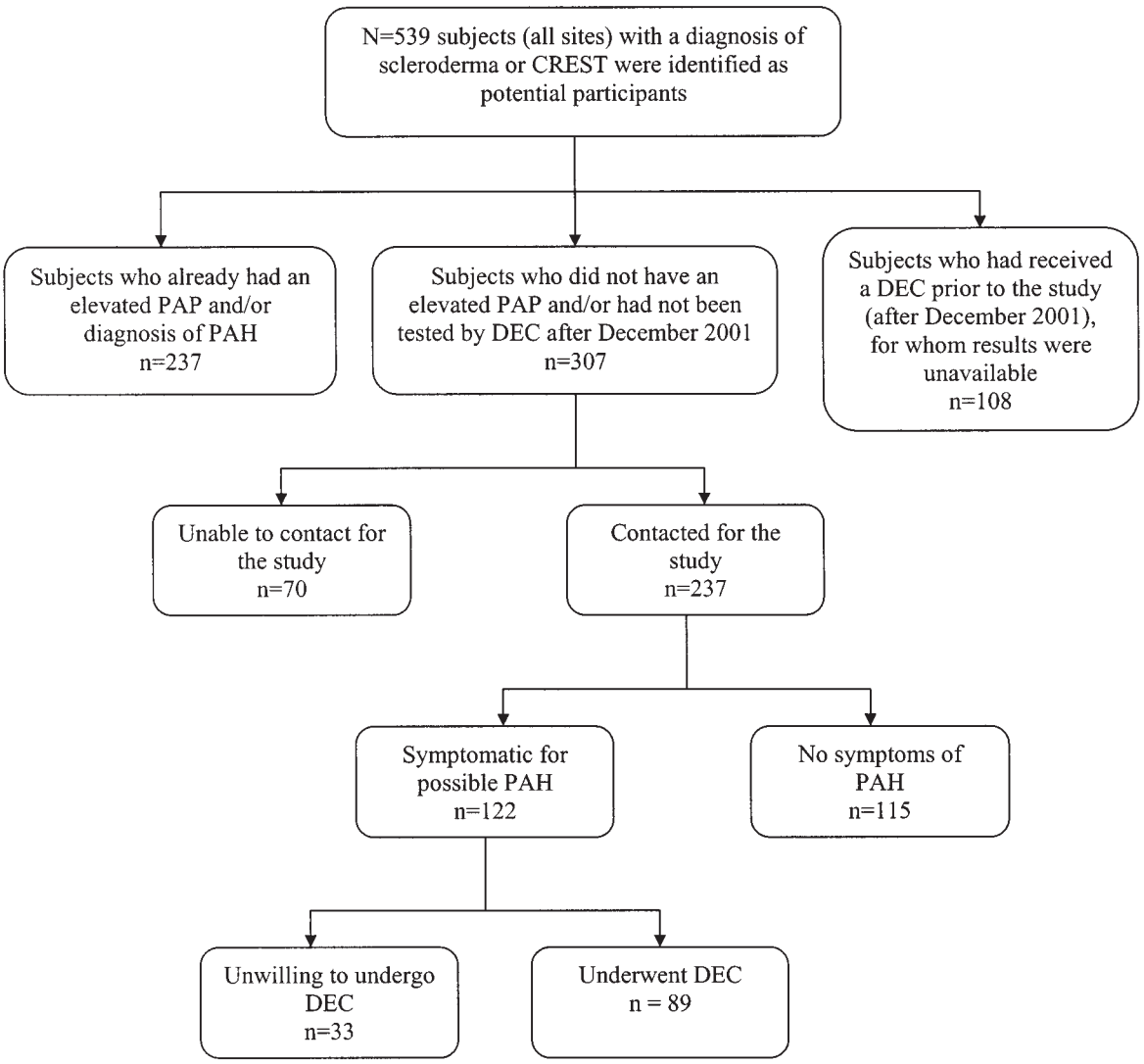

Figure 2. Allocation of SSc and CREST patients in the study.

treatment during the study period, likely due to their New York Heart Association class and/or lack of further confirmatory PAH testing. For the newer agents, only 7% patients received epoprostenol, while 3% received bosentan. Conventional therapies for PAH were uncommon; 10% received calcium channel blockers, 9% received anticoagulants, 2% digoxin, 12% diuretics, and 10% oxygen (likely used in the most severe cases).

Logistic regression methods were applied to determine the probability of elevated PAP in terms of the following variables: age, time from initial SSc diagnosis, sex, and type of SSc. The only statistically significant factor was age, with a customized odds ratio equal to 1.3 (95% CI 1.1 to 1.5), expressed in terms of a change in age of 10 years.

DISCUSSION

Elevated PAP as measured by DEC was common in both patients with limited and those with diffuse SSc. This study found that more than 29% of all patients followed for SSc had high pulmonary artery pressures. Limitations of this study include the exclusion of patients with dyspnea or fatigue who did not agree to be screened (n = 33), as well as those asymptomatic patients that could have high PAP (n = 115). However, it is unlikely that the majority of those with no perceived symptoms would have clinically important PAH (as they would not even be in Class II). We did not pretest our screening questionnaire and do not know from other SSc populations if a prevalence of dyspnea and/or fatigue would be this high. The wide range of prevalence estimates of elevated PAP within the study sites are likely attributable to the difference in the frequency of performing DEC and referral biases. In general, centers with lower numbers of patients included in this study had larger retrospective prevalence estimates of elevated PAP than larger centers.

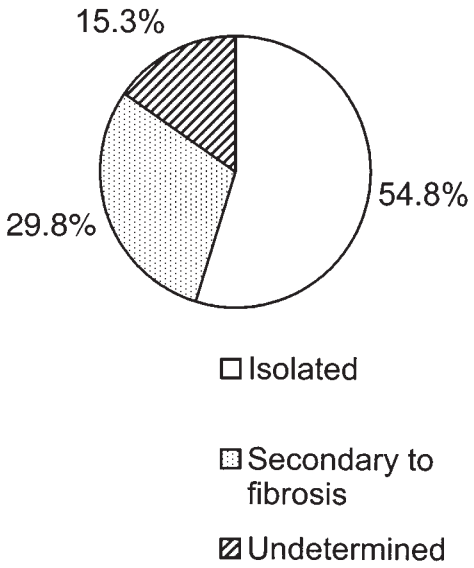

Figure 3. Pulmonary arterial hypertension (PAH) disease etiology.

Given the poor prognosis associated with PAH, particularly in more advanced stages, early identification of these patients is an important goal in SSc management. The most useful noninvasive test for the screening of PAH is the DEC, and annual screening as recommended by the WHO guidelines[23] is currently not performed in most SSc patients in Canada. Indeed, about 15% of all patients without known PAH or elevated PAP and without a recent echocardiogram were found to have elevated systolic PAP. Thirty percent of this group with symptoms of dyspnea and fatigue proved to have elevated systolic PAP (36 patients with high PAP from the 122 symptomatic patients), and 40% of those in this group that underwent DEC had abnormal pulmonary pressure (36 patients from the 89 patients tested by DEC). Although echocardiographic estimations of systolic PAP correlate with right heart catheterization, individual estimates may be inaccurate (and can over- or underestimate PAP)[26], thus emphasizing the importance of confirming the diagnosis of PAH with right heart catheterization in SSc patients with unexplained (moderate) dyspnea.

Chang, *et al* recently reported[27] that 22% of 619 scleroderma patients had a restrictive ventilatory defect. Nineteen percent had isolated pulmonary hypertension on echocardiography and 18% had a restrictive ventilatory defect and pulmonary hypertension. They concluded that those patients with pulmonary hypertension and lung disease were more likely to have diffuse disease, but had a prognosis similar to those with isolated pulmonary hypertension[27]. They also reported in a separate study that older age at onset of scleroderma was a risk factor for PAH[28].

A motivating factor for the identification of PAH in patients with SSc is the availability of effective interventions. Epoprostenol (continuous intravenous infusion), treprostinil (continuous subcutaneous infusion), and bosentan (oral endothelin receptor antagonist) have demonstrated efficacy in prospective randomized studies in patients with PAH. Badesch, *et al* have shown that epoprostenol therapy improved exercise capacity, hemodynamics, dyspnea, and WHO functional class compared to conventional treatment in 111 SSc patients with moderate to severe PAH[24]. A trial with treprostinil that included patients with SSc showed similar benefit[29]. Patients with primary pulmonary hypertension and PAH related to SSc were studied in a randomized trial comparing bosentan to placebo, and the bosentan group experienced a significant improvement in exercise capacity, dyspnea, and WHO functional class and less clinical worsening (defined as death, lung transplant, hospitalization, or initiation of epoprostenol therapy) compared to placebo[25].

The actual prevalence of PAH in SSc by right heart catheterization is thought to be lower than an estimation by DEC alone. Mukerjee, *et al* found 12% of 794 scleroderma patients to have PAH based on right heart catheterization[30]. This proportion is comparable to our group who received more aggressive, newer therapies for PAH.

A high index of suspicion is important and a more vigorous system of routine screening with Doppler echocardiography should be advocated in rheumatology centers across Canada. SSc patients at risk should be identified, to include those with dyspnea or fatigue and those having a very low or progressively declining pulmonary diffusion capacity[22]. We found no easily measured clinical risk factors for those who had elevated PAP. It is unknown what proportion of SSc patients with an elevated estimated PAP, as measured by DEC, will progress to develop clinically important PAH and at what rate, so further studies are warranted, particularly if earlier intervention improves the longterm prognosis. Risk factor identification for those who will develop moderate or severe PAH is needed.

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